Citation:

Lemaitre RN, King IB, Sotoodehnia N, Rea TD, Raghunathan TE, Rice KM, Lumley TS, Knopp RH, Cobb LA, Copass MK, Siscovick DS. Red blood cell membrane alpha-linolenic acid and the risk of sudden cardiac arrest. *Metabolism.* 2009 Apr;58(4):534-40.

PubMed ID: 19303975

Study Design:

Case-Control Study

Class:

C - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To investigate the association of red blood cell membrane α-linolenic acid with sudden cardiac arrest risk in a population-based case-control study.

Inclusion Criteria:

- Cases, aged 25 to 74 years, were out-of-hospital sudden cardiac arrest married residents attended by paramedics in Seattle and suburban King County, Washington between October 1988 and September 2005
- Controls were matched to cases by age, sex and calendar year and were randomly identified from the community
- All participants were free of prior clinically diagnosed heart disease

Exclusion Criteria:

- Patients with cardiac arrest due to a noncardiac cause
- Patients for whom the paramedics were unable to draw a blood sample at the time of the arrest
- Patients with a history of clinically recognized heart disease or life-threatening comorbidities
- Users of fish oil supplements
- Patients whose blood samples could not be analyzed due to fatty acid oxidation

Description of Study Protocol:

Recruitment

- Cases were out-of-hospital sudden cardiac arrest married residents attended by paramedics in Seattle and suburban King County, Washington between October 1988 and September

2005; cases were identified from emergency service incident reports, death certificates, medical examiner reports, and autopsy reports and spouses were contacted
- Controls were randomly identified from the community using random digit dialing

Design: Case-control study

Blinding used (if applicable): Laboratory analyses were conducted by technicians blinded to case and control status.

Intervention (if applicable): not applicable

Statistical Analysis

- Distribution of risk factors among cases and controls were compared using 2-sample t tests for continuous variables and Pearson chi-squared test for categorical variables
- Risk factor distribution across quartiles of α-linolenic acid levels among controls were compared using ANOVA
- The associations of α-linolenic acid with other fatty acids among controls were assessed with Pearson correlation coefficients
- Conditional logistic regression was used to obtain odds ratios of sudden cardiac arrest associated with increasing levels of red blood cell membrane α-linolenic acid
- Statistical significance was assessed with the likelihood ratio test
- Odds ratios associated with upper quartiles of α-linolenic acid levels were obtained from models with indicator variables for the quartiles using the lowest quartile as reference

Data Collection Summary:

Timing of Measurements

- Blood was obtained at the time of cardiac arrest for cases or at the time of interview for controls.
- Food frequency questionnaire was administered to 81 controls

Dependent Variables

- Sudden cardiac arrest risk

Independent Variables

- Red blood cell membrane α-linolenic acid
- Blood specimens were processed and submitted to gas chromatography

Control Variables

- Age
- Sex
- Calendar year
- Smoking
- Diabetes
- Hypertension
- Education
- Physical activity
- Weight

- Height
- Total fat intake assessed with Northwest Lipid Research Clinic Fat Intake Scale
- Intake of long-chain n-3 fatty acids from seafood assessed with Seafood Intake Scale

Description of Actual Data Sample:

Initial N: Spouses of 289 eligible cases, 415 controls

Attrition (final N): 265 cases and 415 controls (1-2 controls per case)

Age: aged 25 - 74 years; mean age cases = 58.4 ± 10.5 years, controls = 57.1 ± 10.4 years

Ethnicity: Cases = 88.7% white, controls = 92.1% white

Other relevant demographics:

Anthropometrics: matched for age (within 7 years), sex and calendar year

Location: Seattle, Washington

Summary of Results:

Key Findings

- Mean red blood cell α-linolenic acid levels were higher in cases than controls, and mean levels of DHA and EPA were lower in cases than controls
- Mean levels of *trans*-18:2 were also higher in cases
- Higher membrane α-linolenic acid was associated with a higher risk of sudden cardiac arrest
- Other traditional risk factors for sudden cardiac arrest including current smoking, diabetes, hypertension, and family history of myocardial infarction or sudden cardiac death were more prevalent among cases than controls
- Cases were less likely to have formal education beyond high school and were less likely to engage in leisure time physical activity
- α-linolenic acid levels were not related to age, diabetes, hypertension, smoking and education, but they were associated with female sex, lower body weight, and lower fat index score
- α-linolenic acid levels were positively associated with red blood cell membrane levels of linoleic acid (r = 0.39), trans-18:2 (r = 0.22), and EPA (r = 0.16) but not with DHA (r = 0.04).
- After adjustment for matching factors and smoking, diabetes, hypertension, education, physical activity, weight, height and total fat intake, the odds ratios corresponding to increasing quartiles of α-linolenic acid were 1.7 (95% confidence interval: 1.0 - 3.0), 1.9 (95% confidence interval: 1.1 - 3.3) and 2.5 (95% confidence interval: 1.3 - 4.8) compared with the lowest quartile
- The association was independent of red blood cell levels of long-chain n-3 fatty acids, trans fatty acids, and linoleic acid.
- An increase in α-linolenic acid corresponding to 1 standard deviation was associated with 32% higher risk of sudden cardiac arrest (odds ratio = 1.32, 95% confidence interval: 1.07 - 1.63) after adjustment for confounding variables.

Author Conclusion:

In conclusion, we observed an association of red blood cell membrance levels of α-linolenic acid with higher risk of sudden cardiac arrest. We hypothesize that membrane α-linolenic acid is a marker of poor conversion to long-chain n-3 PUFAs. Further work is needed to confirm the study findings in other populations and to explore whether the association of dietary α-linolenic acid with sudden cardiac arrest is affected by variation in metabolic processes, such as incorporation into membrane phospholipids and conversion to EPA.

Reviewer Comments:

Food frequency questionnaire only administered to 81 controls; some missing values for cases and controls were imputed. Authors note that associations of diet and membrane levels of ALA with sudden cardiac arrest could not be contrasted, and there were incomplete adjustments for saturated fat intake.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes

2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	Yes
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	Yes
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A

5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	Yes
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	N/A
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	N/A
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes

8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes